PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness of two psychological interventions for pain management, emotional regulation and promotion of quality of life among adult Portuguese men with Haemophilia (PSY-HaEMOPEQ): study protocol for a single-center prospective randomized controlled trial
AUTHORS	Pinto, Patrícia; Paredes, Ana; Costa, Patrício; Carvalho, Manuela; Lopes, Manuela; Fernandes, Susana; Pedras, Susana; Almeida, Armando

VERSION 1 - REVIEW

REVIEWER	***Michelle L. Witkop DNP, FNP-BC*** Northern Regional Bleeding Disorders Center at Munson Medical Center 1105 Sixth Street Traverse City, MI USA 49686
REVIEW RETURNED	10-Apr-2017

GENERAL COMMENTS	BMJ Comments-MLW Page 2/29 Line 8 – haemophilia in this context should not be capitalized throughout the manuscript. Line 11 – same. I won't keep repeating. Line 29 – weakly should be "weekly" Page 4/29 Line 5/6 – need a reference Line 15 – very subjective….."in a very "clearheaded editorial"…. Just state, "In an editorial…" Line 54 - hypnosis in this context should not be capitalized throughout the manuscript. Page 5/29 Line 50/51 beginning with "Globally.."…Needs a reference. Page 6/29 The Objective of the study states this study was for Portuguese PWH while the official title states simply "PWH". I think the title needs to reflect that this was a single center study and be more focused rather than expansive to include "all PWH". I would suggest the title be reworded as such: "Effectiveness of two psychological interventions for prevention and management of pain, emotional regulation and promotion of quality of life among adult Portuguese men with Haemophilia (PSY-HaEMOPEQ): study protocol for a single-center prospective randomized controlled trial" Page 7/29 Line 55 – enrollment is spelled incorrectly

	Page 8/29 Line 57/58 - …will be closely monitored, either by self-report or by collecting information from clinical records (it is either/or not either/and) Page 12/29 Line 9/10 – Is the Stanford Hypnotic Susceptibility Scale for all participants or only for those in the hypnosis subgroup? It was not listed in Figure 1. Line 47 – Multidimensional Pain Tool – I think you need to clearly state throughout the survey that this is a non-validated tool. There is one statement at the end of this paragraph that states you are in the process of validation during this study but this needs to be more clearly stated throughout the study. Since this is a non-published Page 13/29 Line 8 – A36Hemofilia-QoL – You should state this is a validated tool. I also think there is inappropriate capitalization of words here. Line 15 – Hospital Anxiety and Depression Scale – Again, this needs to state this is a validated tool. Plus the name implies it is for hospital use and these are outpatients. So please add a statement or two about its applicability to the community. https://www.gl-assessment.co.uk/products/hospital-anxiety-and-depression-scale-hads/ Line 24 - ?recur? I think the authors mean refer. Line 36 – One sentence in each category to refer whether the scale is validated or not given you are using both validated and non-validated tools. Final comments – the protocol appears to be appropriate and meets all the SPIRIT checklist guidelines. I do question the ability of this protocol to "prevent" pain in a hemophilia patient. Especially when the inclusion criteria require the patient already have established chronic pain. You can manage the pain they have but you can't prevent pain. I would suggest this be removed. With that, the title should read: "Effectiveness of two psychological interventions for the management of pain, emotional regulation and promotion of quality of life among adult Portuguese men with Haemophilia (PSY-HaEMOPEQ): study protocol for a single-center prospective randomized controlled trial"

REVIEWER	***Katharina Holstein*** University Medical Centre Hamburg-Eppendorf Germany
REVIEW RETURNED	01-May-2017

GENERAL COMMENTS	This prospective randomised controlled trial is an important study with the aim to improve treatment for patients with Haemophilia (PWH). The manuskript is well written and describes clearly objectives and methods of the study protocol. One concern is that from the description of the pain questionnaire it is not completely clear how assessment and statistical analysis of the primary outcome parameter will be done. Comments: Abstract, page 2, line 17: You state that the investigation aims to evaluate ...interventions for prevention and management of pain. It is not clear how effect on pain prevention should be measured because an inclusion criterion is presence of chronic pain.

	page 7, line 24, inclusion criteria: chronic pain is an inclusion criterion but there is no exact definition of chronic pain provided and how it will be assessed (baseline pain questionnaire?). Please add some information. Also presence of anxiety and depressive symptoms is an inclusion criterion, assessed by the HADS. Reading the text from line 40-56 it is not clear if baseline assessment is used to check the inclusion criteria and patients could be excluded after informed consent because they do not have chronic pain or depressive symptoms. Figure 1 suggests that inclusion/exclusion criteria will be checked after screening. So please clarify the exact procedure. page 8, line 19: CBT and HyP are different psychologilcal interventions so I believe that at least those patients who know something about these techniques would recognise which kind of intervention they are allocated to after start of the intervention. So how could blinding concerning the type of intervention be guaranteed? page 8, line 54: "factor replacement consumption" should be reworded to "(clotting) factor concentrate consumption" or "amount of factor replacement". The same in the abstract, on page 11, line 44 and page 12, line 44. page 12, line 42: you write "age of diagnosis", but probably "age at time of diagnosis" is meant page 12, line 47: as pain is the primary outcome of the study the pain questionnaire needs to be described in more detail or should be provided as appendix because it is not a validated and published questionnaire yet. Additionally it is necessary to describe how it will be evaluted for statistical analysis. Will there be a global pain score and if yes, how will it be composed - or will each variable like for example pain intensity or frequency be analysed seperately. Not all of the items included in the questionnaire are quantitative (e.g. treatment strategies), so please clarify how they account to the analysis. page 14, line 10: I agree that functional orthopaedic assessment is important to measure the effect of the interventions on orthopaedic joint status and function or to exclude deterioration as cause for increasing pain and can be done without risks for the patient. But why is the radiological score necessary already after 3 months? Please describe the rationale for this to understand why it is neccessary to expose patients again to radiation. Do you expect early morphological changes already after 3 months? Or is the rationale of the early re-evalutaion to exclude that early, radiologically detectable progression of arthropthy leads to more pain or confounds the effect of the interventions? This should be clarified.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer’s comments

1. Response to Reviewer: 1

Reviewer Name: Michelle L. Witkop DNP, FNP-BC

Institution and Country: Northern Regional Bleeding Disorders Center at Munson Medical Center, 1105

Sixth Street, Traverse City, MI USA 49686

Page 2/29
1.1. Line 8 – haemophilia in this context should not be capitalized throughout the manuscript.
Author's answer: We thank the Reviewer for the correction on the appropriate capitalization. We have made changes in the manuscript, only capitalizing at the beginning of sentences, in the title, and when referring to "Haemophilia Center" and "Multidimensional Haemophilia Pain Questionnaire". Changes to capitalization are marked in red on the first time the change was made.

1.2. Line 11 – same. I won't keep repeating.
Author's answer: We have changed this throughout the entire paper, but only marked in red in the first change made.

1.3. Line 29 – weakly should be "weekly"
Author's answer: We acknowledge the Reviewer for noticing and pointing this out. We have already corrected the typo.

Page 4/29
1.4. Line 5/6 – need a reference
Author's answer: Two references were added to this sentence: Lobet et al., 2014 (1) and Merskey, 1986 (9).

1.5. Line 15 – very subjective….."in a very "clearheaded editorial"…. Just state, "In an editorial…"
Author's answer: The suggested change has been made.

1.6. Line 54 - hypnosis in this context should not be capitalized throughout the manuscript.
Author's answer: Again, we thank the Reviewer for corrections on capitalization. This has been changed throughout the article, except in the start of a sentence or when specifically referring to the name of the intervention, similarly to what happens when we refer to "Cognitive-Behavioral Therapy".

Page 5/29
1.7. Line 50/51 – beginning with "Globally.."…Needs a reference.
Author's answer: The reviewer is absolutely right. The reference for this sentence is Pai et al., 2016 (61), but in fact this was not clear. We have slightly changed the sentence and replaced the final mark with a comma, so that the reference (61) concerns our entire statement on integrated care.

1.8. Page 6/29 – The Objective of the study states this study was for Portuguese PWH while the official title states simply "PWH". I think the title needs to reflect that this was a single center study and be more focused rather than expansive to include "all PWH". I would suggest the title be reworded as such:
"Effectiveness of two psychological interventions for prevention and management of pain, emotional regulation and promotion of quality of life among adult Portuguese men with Haemophilia (PSY-HaEMOPEQ): study protocol for a single-center prospective randomized controlled trial"
Author's answer: This is a very relevant remark. In fact, it would be more straightforward if the title reflected the target population of the RCT, so this has been changed, as suggested.

Page 7/29
1.9. Line 55 – enrollment is spelled incorrectly
Author's answer: This has been changed.

Page 8/29
1.10. Line 57/58 - …will be closely monitored, either by self-report or by collecting information from

clinical records (it is either/or not either/and)
Author's answer: Thanks for the correction. This has been changed accordingly.

1.11. Page 12/29 Line 9/10 – Is the Stanford Hypnotic Susceptibility Scale for all participants or only for those in the hypnosis subgroup? It was not listed in Figure 1.
Author's answer: The Reviewer is right in pointing this out. In fact, the Stanford Hypnotic Susceptibility Scale (SHSS) will be administered at T0 (baseline assessment) to all patients, in order to later control for a possible effect of hypnotic susceptibility on inter-group differences. We also included it in Table 1 and hope the procedure is now clear to the reader.

1.12. Line 47 – Multidimensional Pain Tool – I think you need to clearly state throughout the survey that this is a non-validated tool. There is one statement at the end of this paragraph that states you are in the process of validation during this study but this needs to be more clearly stated throughout the study. Since this is a non-published
Author's answer: In order to clarify that the questionnaire is not yet validated, but that the validation process is ongoing, we made some changes to its description, further detailing its content, in the assessment measures section (page 12-13). We state that the questionnaire was developed by our team and that it is currently going through the validation process after being used, in its experimental version, on the first Portuguese haemophilia national survey, conducted by our team. We also added that its development was based on an extensive literature review (on haemophilia pain and existing pain questionnaires), expert opinion (haemophilia doctors) and patient feedback (pilot study), which allowed for further refinement of item content and wording. Therefore, we are confident that this is a good measure of haemophilia-related pain and that it is going to fill a recognized gap in this area. The collection of surveys just ended now and we are now beginning data analysis, in order to further evaluate the questionnaire measurement properties and publish the validation paper. At the time of the beginning of this trial the final version will be certainly ready to use.

Page 13/29
1.13. Line 8 – A36Hemofilia-QoL – You should state this is a validated tool. I also think there is inappropriate capitalization of words here.
Author's answer: More specific information was added concerning validation data of the A36 Haemophilia QoL. The questionnaire was originaly developed and validated in Spain, showing good measurement properties. The Portuguese version is still under validation process (similarly to the abovementioned pain questionnaire) after a complete translation back-translation process by certified translators. However, given the very close cultural context of both countries we believe the questionnaire will show similar appropriate characteristics. We have removed the capitalization when naming the subscales of the A36 Haemophilia QoL and the other questionnaires.

1.14. Line 15 – Hospital Anxiety and Depression Scale – Again, this needs to state this is a validated tool. Plus the name implies it is for hospital use and these are outpatients. So please add a statement or two about its applicability to the community.
https://www.gl-assessment.co.uk/products/hospital-anxiety-and-depression-scale-hads/
Author's answer: Despite the name of the scale, the questionnaire was originally developed in the setting of a general medical hospital outpatient clinic. Therefore, we believe its use is appropriate in this RCT, notwithstanding its validation in other populations. We added this information when describing HADS, so that this is clear to all readers (page 14). We also added to the original reference, the reference concerning the validation of the Portuguese version of HADS.

1.15. Line 24 - ?recur? I think the authors mean refer.
Author's answer: Thanks for pointing out that this was not clear. We changed it to "use".

1.16. Line 36 – One sentence in each category to refer whether the scale is validated or not given you

are using both validated and non-validated tools.
Author's answer: This information was added to the description of all measures, in order to clarify which versions are validated or not.

1.17. Final comments – the protocol appears to be appropriate and meets all the SPIRIT checklist guidelines. I do question the ability of this protocol to "prevent" pain in a hemophilia patient. Especially when the inclusion criteria require the patient already have established chronic pain. You can manage the pain they have but you can't prevent pain. I would suggest this be removed. With that, the title should read:
"Effectiveness of two psychological interventions for the management of pain, emotional regulation and promotion of quality of life among adult Portuguese men with Haemophilia (PSY-HaEMOPEQ): study protocol for a single-center prospective randomized controlled trial"
Author's answer: Pain prevention was an initial purpose of this RCT but, in fact, the current protocol is not aimed at pain prevention. Therefore, the title was changed to reflect the aim of pain management in patients with already established chronic pain.

2. Response to Reviewer: 2

Reviewer Name: Katharina Holstein
Institution and Country: University Medical Centre Hamburg-Eppendorf, Germany

This prospective randomised controlled trial is an important study with the aim to improve treatment for patients with Haemophilia (PWH). The manuskript is well written and describes clearly objectives and methods of the study protocol. One concern is that from the description of the pain questionnaire it is not completely clear how assessment and statistical analysis of the primary outcome parameter will be done.
Author's answer: In order to shed some light on the questionnaire used to assess pain, we expanded the description of the Multidimensional Haemophilia Pain Questionnaire, in the assessment measures section (page 12-13). A more detailed description of the dimensions assessed can now be found. We hope the changes are enough to clarify both content and statistical analysis of the outcome.

Comments:
2.1. Abstract, page 2, line 17: You state that the investigation aims to evaluate ...interventions for prevention and management of pain. It is not clear how effect on pain prevention should be measured because an inclusion criterion is presence of chronic pain.
Author's answer: We acknowledge the Reviewer for this comment, which gave us the opportunity to clarify the main objective of our paper. In fact, we initially aimed to test an intervention focused on pain prevention, in the scope of a secondary prevention action. By adding presence of chronic pain to the inclusion criteria this is no longer possible and, therefore, we have changed the title, removing the allusion to pain prevention, and better clarifying the aim of the RCT.

2.2. page 7, line 24, inclusion criteria: chronic pain is an inclusion criterion but there is no exact definition of chronic pain provided and how it will be assessed (baseline pain questionnaire?). Please add some information.
Author's answer: For the purpose of this RCT, we adopted the definition of chronic pain provided by the European Haemophilia Therapy Standardization Board (Holstein et al., 2012), as is now stated in the inclusion criteria section (page 6-7). This is assessed before enrollment, by the research team clinicians, who are familiar with the definition and will directly ask the patient about the duration and frequency of their pain, to establish chronicity.

2.3. Also presence of anxiety and depressive symptoms is an inclusion criterion, assessed by the

HADS. Reading the text from line 40-56 it is not clear if baseline assessment is used to check the inclusion criteria and patients could be excluded after informed consent because they do not have chronic pain or depressive symptoms. Figure 1 suggests that inclusion/exclusion criteria will be checked after screening. So please clarify the exact procedure.
Author's answer: While reviewing the paper with the research team, this point raised a discussion concerning the HADS inclusion criteria and, after careful reflection, it was decided that the HADS score will be removed from inclusion criteria in the RCT. This is due to the fact that anxiety and depression are not primary outcome measures and we believe the intervention will be beneficial despite baseline anxiety/depression scores. The remaining inclusion criteria will be checked by the clinicians who are part of the research team before enrollment. They will briefly explain the study and assess the criteria, and only those patients who fill the criteria will be referred to the investigator, who further explains study objectives, clarifies concerns or doubts and performs T0 assessment. This procedure was detailed on the manuscript – participants and procedures section (page 6-7).

2.4. page 8, line 19: CBT and HyP are different psychologilcal interventions so I believe that at least those patients who know something about these techniques would recognise which kind of intervention they are allocated to after start of the intervention. So how could blinding concerning the type of intervention be guaranteed?
Author's answer: The Reviewer is right in raising this concern. We believe that most patients are not at all familiar with different types of psychological intervention, but since we cannot ascertain this for sure, we therefore cannot guarantee blinding to type of intervention. However, we maintain that the investigators will not tell the patient if he is on "Cognitive-Behavioral Therapy" or "Hypnosis" group, because we believe this would elicit further bias and maybe raise some expectations or prejudice. This has been modified accordingly, in the randomization and allocation section (page 7-8).

2.5. page 8, line 54: "factor replacement consumption" should be reworded to "(clotting) factor concentrate consumption" or "amount of factor replacement". The same in the abstract, on page 11, line 44 and page 12, line 44.
Author's answer: We thank the Reviewer for this correction. It has been changed as suggested.

2.6. page 12, line 42: you write "age of diagnosis", but probably "age at time of diagnosis" is meant
Author's answer: Yes, this is true and has been changed.

2.7. page 12, line 47: as pain is the primary outcome of the study the pain questionnaire needs to be described in more detail or should be provided as appendix because it is not a validated and published questionnaire yet. Additionally it is necessary to describe how it will be evaluted for statistical analysis. Will there be a global pain score and if yes, how will it be composed - or will each variable like for example pain intensity or frequency be analysed seperately. Not all of the items included in the questionnaire are quantitative (e.g. treatment strategies), so please clarify how they account to the analysis.
Author's answer: We provided further detail on the pain questionnaire (MHPQ) and on it subscales. As we have detailed, there is no global pain score. Answer format of each dimension is described in the manuscript. As the Reviewer pertinently points out, not all items are quantitative and thus it remains to clarify how they will be analyzed in terms of statistical strategy, an issue which is most important since pain is one of the primary outcomes of this study. Actually, not all dimensions of pain questionnaire will be treated as a primary outcome. The ones which will are pain frequency, intensity and interference, all of them handled as quantitative variables and thus statistically treated as described in the section concerning Data Analysis Plan of the manuscript. We have now added in the manuscript that these three dimensions are the ones considered for effects of primary outcome analysis (page 11).

2.8. page 14, line 10: I agree that functional orthopaedic assessment is important to measure the

effect of the interventions on orthopaedic joint status and function or to exclude deterioration as cause for increasing pain and can be done without risks for the patient. But why is the radiological score necessary already after 3 months? Please describe the rationale for this to understand why it is neccessary to expose patients again to radiation. Do you expect early morphological changes already after 3 months? Or is the rationale of the early re-evalutaion to exclude that early, radiologically detectable progression of arthropthy leads to more pain or confounds the effect of the interventions? This should be clarified.
Author's answer: The radiological assessment was included at 3 month follow-up as a measure of short/medium term efficacy of the intervention, in order to assess if there are already any observable orthopedic changes at this time. By repeating the evaluation at 12 months we hope to conclude if the intervention had long term effects and if these are maintained through time. At the same time both evaluation will also be valuable to exclude increased joint damage as cause for increased pain.

VERSION 2 – REVIEW

REVIEWER	Michelle L. Witkop DNP FNP BC Northern Regional Bleeding Disorders Center @ Munson Medical Center USA
REVIEW RETURNED	05-Jun-2017

GENERAL COMMENTS	The authors have made the requested revisions. This appears to be an interesting study and I am excited to see the outcome.

REVIEWER	Katharina Holstein University Medical Centre Hamburg-Eppendorf, Hamburg, Germany
REVIEW RETURNED	12-Jun-2017

GENERAL COMMENTS	The reviewers comments and concerns have been addressed sufficiently.